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(54) Verfahren zur Herstellung mehrfach substituierter Acylbenzole.

(57) The present invention relates to a method of preparing poly-substituted acylbenzenes. The method comprises reacting acylhalides or equivalents with poly-substituted benzene in the presence of an acylating catalyst comprising a perfluoro sulfonic acid polymer.

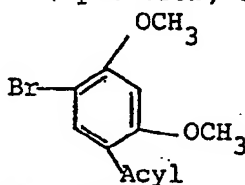
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This invention relates to a method of preparing poly-substituted acylbenzenes and more particularly to synthesizing these acylbenzenes by means of a perfluoro sulfonic acid polymer acylating catalyst.

5 When an acyl halide or equivalent is reacted with 2-bromo-1, 3-dimethoxybenzene to form the corresponding acylbenzene it has been found that rearrangement products either predominate or at least are present as major contaminants when usual acylating or Friedel-Crafts catalysts
10 are employed. Such rearrangement products involve bromine migration from the 2 to 4 position, e.g.,

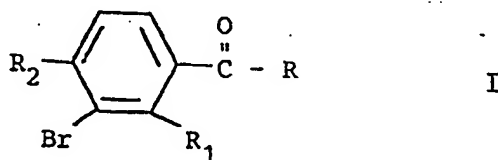


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As reported by G.A. Olah, et al, in Synthesis, 1978, 672, a solid perfluorinated resin sulfonic acid, commercially available from E.I. DuPont de Nemours as ^(R)Nafion H, can be employed as an acylating catalyst in reactions between acyl halides, anhydrides, or mixtures of acids and
20 their anhydrides and other substituted benzenes. However, it has not heretofore been reported or suggested that such a perfluorinated resin sulfonic acid could function to prevent the formation of rearrangement products when 2-bromo-
25 1,3-dimethoxybenzene is employed.

Therefore, the present invention is directed to a method of preparing poly-substituted acylbenzenes of the formula I

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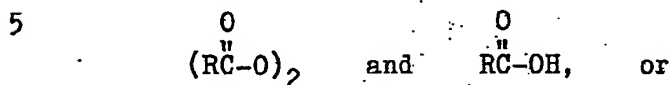


and more particularly to synthesizing the acylbenzenes by
35 means of a perfluorosulfonic acid polymer acylating catalyst.

The method comprises reacting

a) a compound of the formula $\text{RC}-\overset{\text{O}}{\underset{\text{O}}{\text{Hal}}}$, or

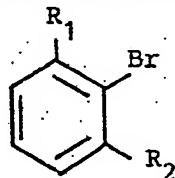
b) a mixture of the compounds of the formula



c) a compound of the formula $(\text{RC}-\overset{\text{O}}{\underset{\text{O}}{\text{O}}})_2\text{O}$

wherein R is C_1-C_6 -alkyl or a mono- or polycyclic aromatic
10 or a heteroaromatic radical which may be substituted with
the radicals X_m and Y_n where X and Y are the same or different
and represent halogen, C_1-C_6 -alkyl, C_1-C_6 -alkoxy, C_1-C_6 -alkylthio,
trifluoromethyl or nitro, and m and n are the same or different integers of 1 or 2,

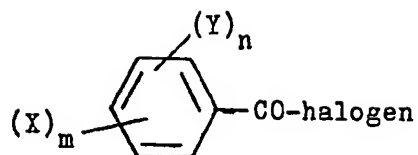
15 with a compound of the formula II



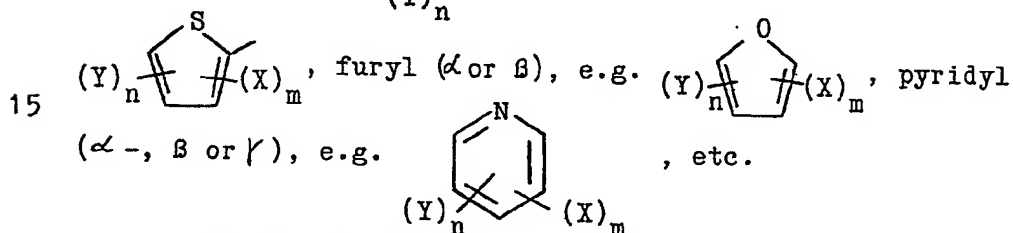
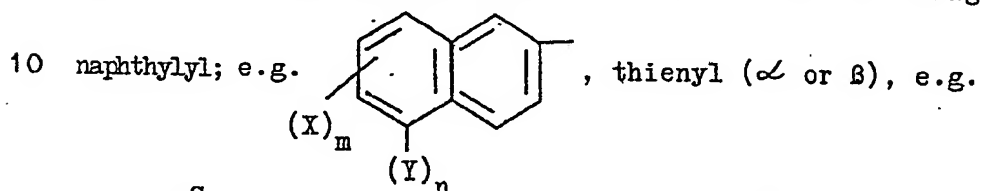
20 wherein R_1 and R_2 are the same or different and represent
 C_1-C_6 -alkoxy or hydroxy, in the presence of an acylating
agent comprising a perfluorosulfonic acid polymer.

The present invention is described primarily in terms
of acylating bromo-1,3-dimethoxybenzene to form a substituted
25 benzophenone without essentially forming a contaminating
rearrangement acylating product; however, it will be understood
that such description is exemplary only and is for purposes of
exposition and not for purposes of limitation. It will be readily
appreciated that the inventive
30 concept described is equally applicable to acylating 2-bromo-
1,3-dimethoxybenzene or 2-bromo-1,3-dihydroxybenzene with an
acylhalide or equivalent such as an acylanhydride or mixture of
such an anhydride and its corresponding acid.

In the case where the desired product is a benzophenone,
35 a benzoyl halide of the formula



is preferred. Alternatively if a different acylbenzene is
 5 desired an opposite first reactant of one of the above for-
 mulae is selected wherein R is C₁-C₆-alkyl, or another ap-
 propriately substituted aromatic group or a heteroaromatic
 group, including but not limited to one of the following:

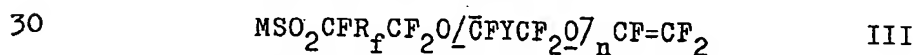


A second reactant of the formula II



where R₁ and R₂ are the same or different and represent C₁-
 alkoxy or hydroxy, e.g., 2-bromo-1, 3-methoxybenzene, is
 25 selected.

A suitable catalyst for the method according to the
 present invention comprises a perfluorosulfonic acid poly-
 mer. Such a polymer comprises a polymeric material obtain-
 ed from a fluorocarbon vinyl ether having the formula III



where R_f represents fluorine or a perfluoroalkyl radical
 having from 1 to 10 carbon atoms, Y represents fluorine or
 the trifluoromethyl radical, n is an integer of 1 to 3 in-
 clusive, and M represents fluorine, the hydroxyl radical,
 35 the amino radical or a radical having the formula -OMe
 where Me is an alkali metal or a quaternary ammonium radi-

cal. The vinyl ether of the formula III is readily homopolymerized or copolymerized to form the catalysts of the present invention. Preferred comonomers for copolymerization include ethylene or halogenated ethylenes. It is to be understood, however, the copolymerization of the vinyl ether are achieved with any ethylenically unsaturated comonomer capable of homopolymerization. Additional fluorinated monomers may also be copolymerized with ethylene or the halogenated ethylenes and the vinyl ethers, such third monomer being for example a perfluoro alpha-olefin, e.g. hexafluoropropylene, or a perfluoro (alkyl vinyl ether) of the type $\text{CF}_2=\text{CF}-\text{O}-[\text{CF}_2-\text{CH}_2]_{n'}-\text{CF}_3$ where n' is 0 to 5, inclusive.

A preferred catalyst is the group of solid perfluoro sulfonic acid resins or polymers commercially obtained from E.I. DuPont de Nemours and designated as (R) Nafion persulfonic acid products. These (R) Nafion products are copolymers of the above-described vinyl ether and tetrafluoroethylene and are supplied in the salt form, e.g., potassium sulfonate. The salt form is readily converted to the acid form by treatment with a mineral acid, e.g. nitric acid, washing with water and drying at $105^\circ\text{C} - 110^\circ\text{C}$ for about twelve hours. The (R) Nafion persulfonic acids have an empirical formula of $[\text{C}_7\text{H}_{14}\text{O}_4\text{SC}_2\text{H}_4]_Z$, where Z is the number of repeated units, and typically have an equivalent weight within the range of 1100 and 1800.

The above perfluorosulfonic acid resins or polymers and their preparation are fully described in Connally et al., U.S. Patent No. 3,282,875.

The first reactant, the second reactant and the perfluorosulfonic acid polymer catalyst are combined and reacted under the usual Friedel-Crafts reaction conditions. Typically the reactants and catalyst are heated to reflux for a sufficient period of time to achieve the desired acylation, e.g. 22 - 24 hours.

Surprisingly and unexpectedly, the use of the perfluorosulfonic acid polymer catalyst yields the desired pro-

duct, 4-acyl-2-bromo-1,3-dialkoxy- or dihydroxy-benzene, which is free from contamination or formation of significant rearrangement products. This is a surprising and unexpected result since with the usual Friedel-Crafts acylation catalysts, e.g., Lewis acids such as SnCl_4 , ZnCl_2 , AlCl_3 , etc., such rearrangement products are obtained and may often predominate. Such rearrangement products, it is believed, occur because the usual Friedel-Crafts catalysts promote metathesis of the starting material such as 2-bromo-1,3-dimethoxybenzene to yield 4,6-dibromo-1,3-dimethoxybenzene, 2,4-dimethoxybromobenzene and 1,3-dimethoxybenzene. It is this "rearranged starting material" which reacts with the requisite acylating agents to give poor yields of the desired acyl-2-bromo-1,3-dimethoxybenzenes. Surprisingly and unexpectedly the catalysts of the instant process do not cause such rearrangements but promote instead only the desired acylation.

20 EXAMPLE I:

2-Bromo-1,3-dimethoxybenzene [32.60 g; 0.150 mole] and 2-fluorobenzoyl chloride [30.0 g; 0.189 mole] are dissolved in 150 ml of 1,2-dichloro ethane. To this mixture is added ten grams of ^(R)Nafion H, commercially obtained from E.I. DuPont de Nemours. The reaction mixture is brought to reflux and is stirred. After refluxing for 22 hours the catalyst is filtered off and washed with dichloroethane. The combined organic phase is concentrated under reduced pressure to give crystalline material after trituration with hexane. Recrystallization from isopropanol gives 38.5 grams [70 % yield] of 3-bromo-2,4-dimethoxy-2'-fluorobenzophenone, m.p. 88 - 91°C, as the sole benzophenone product.

After an additional recrystallization from isopropanol, the melting point is raised to 92 - 93°C.

Analysis:

Calculated for $C_{15}H_{12}BF_3O_3$: 53.11 % C; 5.7 % H

Found: 53.30 % C; 3.30 % H

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EXAMPLE II:

For comparison purposes, the procedure of Example I is repeated except that the following Friedel-Crafts acylating agents are employed

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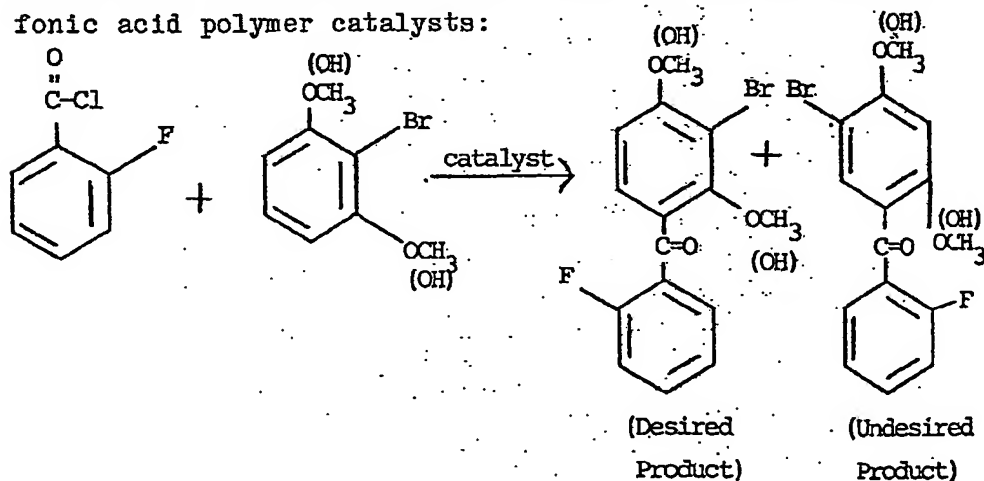
[a] $SnCl_4$;[b] $ZnCl_2$;[c] $AlCl_3$;[d] BBr_3 ;[e] $TiCl_4$.

15

In all cases, either a desired reaction product is not obtained or a mixture of 3-bromo-2,4-dimethoxy-2'-fluorobenzophenone/desired product, 5-bromo-2,4-dimethoxy-2'-fluorobenzophenone [undesired rearrangement product] and/or the various rearranged starting material as heretofore described is obtained.

The following are comparative procedures for the various catalysts employed which graphically illustrate the surprising and unexpected superiority of the perfluorosulfonic acid polymer catalysts:

25



[a] SnCl₄

2-Fluorobenzoyl chloride (1.58 g; 0.010 mole) is dissolved in 15 ml of 1,2-dichloroethane at ice bath temperature. Stannic chloride (2.58 g; 0.010 mole) is added and the reaction is stirred 5 minutes, after which 2-bromo-1,3-dimethoxybenzene is added (2.17 g; 0.010 mole) in 3 ml of 1,2-dichloroethane. After 2 hours, the following mixture of products is obtained, as analyzed by the technique of mass spectrometry/gas chromatography: 2-bromo-1,3-dimethoxybenzene (9.5 %), 4-bromo-1,3-dimethoxybenzene (trace), 4,6-dibromo-1,3-dimethoxybenzene (8.0 %), 2'-fluoro-2,4-dimethoxybenzophenone (11.1 %), 3-bromo-2'-fluoro-2,4-dimethoxybenzophenone (22.9 %), 5-bromo-2'-fluoro-2,4-dimethoxybenzophenone (13.7 %).

[b] ZnCl₂

2-Bromo-1,3-dimethoxybenzene (2.17 g; 0.010 mole) is dissolved in 7 ml of dichloromethane and freshly fused zinc chloride (1.36 g; 0.010 mole) is added. After stirring 15 minutes at room temperature, 2-fluorobenzoyl chloride (1.58 g; 0.010 mole) is added. After stirring 3 days at room temperature, the following mixture is obtained, as analyzed by gas chromatography: 2-bromo-1,3-dimethoxybenzene (9 %), 4-bromo-1,3-dimethoxybenzene (trace), 4,6-dibromo-1,3-dimethoxybenzene (7 %), 2'-fluoro-2,4-dimethoxybenzophenone (22 %), 3-bromo-2'-fluoro-2,4-dimethoxybenzophenone (4 %), 5-bromo-2'-fluoro-2,4-dimethoxybenzophenone (31 %).

[c] AlCl₃

2-Bromo-1,3-dimethoxybenzene (2.17 g; 1.0 mole) and 2-fluorobenzoyl chloride (1.58 g; 1.0 mole) are dissolved in 1,2-dichloroethane and aluminum chloride (1.33 g; 1.0 mole) is added slowly. The reaction mixture is refluxed for 2 hours and then worked up with 5 % hydrochloric acid. In this way a 1:2 mixture of 5-bromo-2'-fluoro-2-hydroxy-

4-methoxybenzophenone and 3-bromo-2'-fluoro-2-hydroxy-4-methoxybenzophenone is obtained, as indicated by nuclear magnetic resonance (NMR). A quantity of this mixture is separated by preparative high pressure liquid chromatography into its two components, 5-bromo-2'-fluoro-2-hydroxy-4-methoxybenzophenone, m.p. 127 - 129°C and 3-bromo-2'-fluoro-2-hydroxy-4-methoxybenzophenone, m.p. 137 - 139°C.

[d] BBr₃

10 2-Bromo-1,3-dimethoxybenzene (4.34 g; 0.020 mole) is dissolved in 15 ml of dichloromethane and 2-fluorobenzoyl chloride (3.16 g; 0.020 mole) is added. This mixture is chilled in an ice bath as boron tribromide is added (3.10 g; 0.020 mole). The reaction is brought to reflux and re-
15 fluxed 16 hours. Thin layer chromatography shows qualitatively an equal mixture of 5-bromo-2'-fluoro-2-hydroxy-4-methoxybenzophenone and 3-bromo-2'-fluoro-2-hydroxy-4-methoxybenzophenone.

20 [e] TiCl₄

2-Bromo-1,3-dimethoxybenzene (2.17 g; 0.010 mole) and 2-fluorobenzoyl chloride (1.58 g; 0.010 mole) are dissolved in 15 ml of 1,2-dichloroethane at -5°C and titanium tetrachloride (1.89 g; 0.010 mole) is added. After 2.5
25 hours gas chromatography shows that 2-bromo-1,3-dimethoxybenzene is entirely consumed and the following mixture of products is present: 4,6-dibromo-1,3-dimethoxybenzene (4 %), 2'-fluoro-2,4-dimethoxybenzophenone (10 %), 3-bromo-2'-fluoro-2,4-dimethoxybenzophenone (46 %), 5-bromo-
30 2'-fluoro-2,4-dimethoxybenzophenone (34 %).

E X A M P L E III:

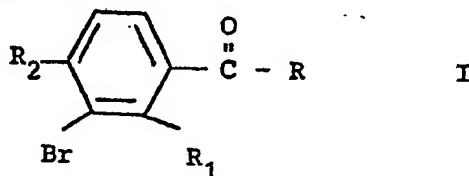
As an illustration of the effect that usual Friedel-
35 Crafts catalysts have on the starting 2-bromo-1,3-dimethoxybenzene, 2.17 g (0.010 mole) of this material is dis-

solved in 15 ml of 1,2-dichloroethane and ferric chloride (1.62 g; 0.010 mole) is added. After 30 minutes at room temperature gas chromatography shows that 2-bromo-1,3-dimethoxybenzene is almost completely consumed and a mixture
5 of 4-bromo-1,3-dimethoxybenzene, 1,3-dimethoxybenzene, and 4,6-dibromo-1,3-dimethoxybenzene is in its place.

A similar experiment using the perfluorosulfonic acid polymer catalysts of the instant process in place of the ferric chloride affords only unchanged 2-bromo-1,3-dimethoxybenzene.
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Patent Claims:

1. A method of preparing a poly-substituted acylbenzene having a structural formula I



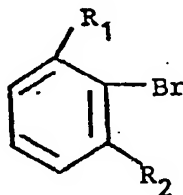
where R_1 and R_2 are the same or different and represent C_1-C_6 -alkoxy or hydroxy, R represents (a) C_1-C_6 -alkyl, or (b) a mono- or polycyclic aromatic or heteroaromatic radical, which radicals may be substituted with X_m or Y_n where X and Y are the same or different and represent halogen, C_1-C_6 -alkyl, C_1-C_6 -alkoxy, C_1-C_6 -alkylthio, trifluoromethyl or nitro, and m and n are the same or different integers of 1 or 2, which comprises reacting

a) a compound of the formula $\overset{\text{O}}{\underset{\text{||}}{\text{R}^n\text{C}}}\text{-halogen}$, or

b) a mixture of the compounds $\overset{\text{O}}{\underset{\text{||}}{(\text{R}^n\text{C}-\text{O})_2\text{O}}$, $\overset{\text{O}}{\underset{\text{||}}{\text{R}^n\text{C}}}\text{-OH}$, or

c) a compound of the formula $\overset{\text{O}}{\underset{\text{||}}{(\text{R}^n\text{C}-\text{O})_2\text{O}}$, where

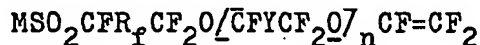
R is as defined above, with a second reactant having the formula II



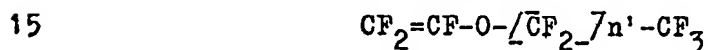
where R_1 and R_2 are as defined above, in the presence of an acylating agent comprising a perfluorosulfonic acid polymer.

2. The method as defined in claim 1 wherein said perfluoro sulfonic acid polymer is

(1) a homopolymer of a vinyl ether having the formula



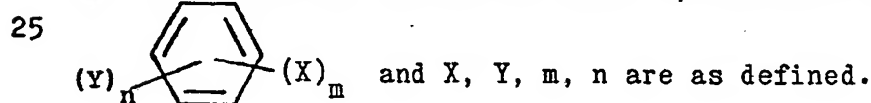
where R_f represents fluorine or a perfluoroalkyl radical having from 1 to 10 carbon atoms, Y represents fluorine or the trifluoromethyl radical, n is an integer of 1 to 3 inclusive, and M represents fluorine, the hydroxyl radical, the amine radical or a radical having the formula $-OMe$ where Me is an alkali metal or a quaternary ammonium radical or (2) a copolymer of the vinyl ether of (1) above and a monomer which may be (a) ethylene, (b) a halogenated ethylene or (c) at least one of monomer selected from ethylene and halogenated ethylenes and at least one monomer selected from perfluorinated alpha-olefins and perfluoro alkyl vinyl ethers having the formula



where n' is 0 to 5.

3. The method as defined in claim 2 wherein R represents phenyl, naphthyl, α -thienyl, β -thienyl, α -furyl, β -furyl, α -pyridyl, β -pyridyl or δ -pyridyl, which may be substituted with X_m or Y_n where X, Y, m and n are as defined.

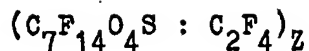
4. The method as defined in claim 3, wherein R is



5. The method as defined in claim 2, wherein said vinyl ether is copolymerized with at least a halogenated ethylene.

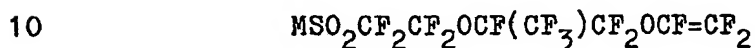
6. The method as defined in claim 5, wherein said vinyl ether is copolymerized with tetrafluoroethylene.

7. The method as defined in claim 6, wherein said copolymer has a structural formula



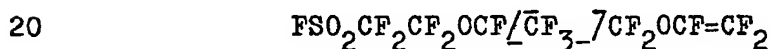
where Z represents a number of repeating units.

8. The method as defined in claim 7, wherein said copolymer has an equivalent weight within the range of 1100 to 1800.
9. The method as defined in claim 1, wherein said catalyst is a copolymer of a vinyl ether having the formula



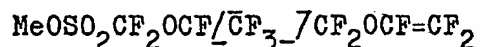
where M represents fluorine, the hydroxyl radical, the amino radical or a radical having the formula -OMe where Me represents an alkali metal or a quaternary ammonium radical, and tetrafluoroethylene.

10. The method as defined in claim 1, wherein said catalyst is a copolymer of a vinyl ether having a formula



and tetrafluoroethylene.

11. The method as defined in claim 1, wherein said catalyst is a copolymer of a vinyl ether having a formula



where Me is an alkali metal or a quaternary ammonium radical and tetrafluoroethylene.



European Patent
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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	G.A. OLAH; "Friedl-Crafts and Related Reactions" vol. III, part 1, 1964; "Acylation and related reactions; INTERSCIENCE PUBLISHERS, New York-London-Sidney; pages 11,12 + Totality + -----		C 07 C 45/45 C 07 C 49/84 B 01 J 31/10
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			C 07 C 45/00 C 07 C 49/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application O: document cited in the application L: citation for other reasons
			§ member of the same patent family, corresponding document
The present search report has been drawn up for all claims			
X	Place of search VIENNA	Date of completion of the search 13-08-1981	Examiner HOFBAUER